Docket No.: 576-008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT OPERATIONS

In re Application of:

Massimo Porro

Serial No.: 09/124,280

Filed: July 29, 1998

Group Art Unit: 1641

Examiner:Minnifield, N.

For: **VACCINES FOR PREVENTION OF GRAM-NEGATIVE INFECTIONS AND ENDOTOXIN RELATED DISEASE**

New York, NY 10036
April 25, 2003

Commissioner for Patents
Washington, DC 20231

SUBSTITUITE APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-8, 10-17, 19-34, 51, 54, 55 and 57-64.

(1) Real party in interest. The real party in interest is BioSynth S.r.l.

(2) Related appeals and interferences. There are no related appeals or interferences.

(3) Status of the claims. Claims 35, 37-50, 52 53 and 56 have been allowed. Claims 1-8, 10-17, 19-34, 51, 54, 55 and 57-64 have been finally rejected over the prior art.

(4) Status of amendments. There are no unentered amendments.

(5) Summary of invention. The invention is directed to a vaccine that is prepared by making an endotoxoid that is made by combining LPS free or in conjugate form, as described at page 2, lines 30-32 of the specification. The vaccine is prepared by

reacting a stoichiometric excess of a peptide of the formula: (a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;
(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2 as described at page 2 of the specification, lines 33-35 and page 3, lines 1-9. The preferred amounts of LPS that is combined with the peptide to make the vaccine according to the invention is from 2-10 to 2-5000 times the weight of LPS of the peptide as defined above as set forth at page 6, lines 24-30 of the specification. The technique of reacting the peptide with the LPS is by combining sterile aqueous solutions for 15 minutes to six hours as set forth in the specification at page 13, lines 15-18. The effective dose of the endotoxoid complex is from 0.1 micrograms to 50 micrograms per kilogram of body weight for a mammal as stated at page 13, lines 18-20 of the specification.

(6) Issues.

Is the rejection of the claims as anticipated under 35 U.S.C.§102(b) a proper rejection?

(7) Grouping of claims. All of the claims may be grouped together for purposes of this appeal except claims 54, 63 and 64 which will be separately discussed.

(8) Argument.

Claims 1-8, 10-17, 19-34, 51, 54, 55 and 57-641-17, 19-34 and 51, which define a vaccine, were rejected under 35 U.S.C.§102(b) as being unpatentable over Porro (WO 95/03327). All

of the claims to the process of making the vaccine have been rejected. In Paper No. 16, the Examiner stated:

> Applicant states that the prior art does not teach using a stoichiometric excess of peptide relative to the lipid moiety and that the method Applicant uses to make the vaccine is not disclosed in the prior art. However, the claimed invention is a vaccine comprising LPS and a peptide which the prior art discloses. Applicant appears to be arguing a process limitation and novel process or improved methods of preparing the vaccine, not the vaccine composition itself.

The claims at issue define a vaccine as a complex obtained by combining LPS ... with a stoichiometric excess of a peptide. The applicant does not contend that the claims to the vaccine are free of a process limitation. The applicant's position is that the process limitation of the claims to the vaccine may be relied upon to point out a novel composition of matter that is not disclosed in the cited reference.

All of the finally rejected claims contain the recitation "a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide, on a weight basis relative to said LPS". The present specification, at page 6, lines 24-32 discloses that the vaccine is prepared by combining LPS with a peptide on specific weight/weight ratios. This language defines novel subject matter over the prior art description of making the vaccine disclosed in the Porro patent publication WO/95/03327 ('327 publication).

The '327 publication at page 7, lines 14-20 states that the vaccines may be made "using stoichiometric amounts of Lipid-A or LPS with the peptide". This does not disclose a vaccine having a "stoichiometric excess of peptide relative to the lipid moiety". In the absence of a disclosure of the presently claimed concept of using a stoichiometric excess of the peptide relative to LPS, it is submitted that the claims do not disclose a vaccine having a stoichiometric excess of a peptide relative to the LPS component. For this reason, the claims define novel subject matter and the rejection under 35 U.S.C.§102(b) should be reversed.

Claims 54 and 63 specify the stoichiometric excess as being a ratio of from 2 to 5000 units of peptide to one unit of LPS or 2 to 2500 units of peptide to one unit of LPS. Claim 64 specifies a ratio of 250 to 2500 of peptide to LPS. These ratios all define a novel vaccine as the prior art is limited to a 1:1 ratio of peptide to LPS.

MPEP §2113 is instructive regarding the manner in which a product-by-process claim is to be considered for patentability. Novelty of a product cannot be based on the novelty of the process. In the present case, the novelty of the product is not based on the novelty of the process. Novelty is predicated on the presence of the stoichiometric excess of the peptide component of the vaccine. The Examiner has not cited any prior art that discloses a vaccine which has a stoichiometric excess of the peptides defined in the claims in combination with LPS. The claims do not include any vaccine suggested by the prior art which were explicitly described as being based on a one to one ratio of the peptide and LPS. The only issue raised in the final rejection was the novelty of the claims. It is submitted that the applicant has demonstrated that the claims are directed to novel vaccines and for this reason, the rejection under 35 U.S.C.§102(b) should be reversed.

The applicant has disclosed an advance in the useful art of making vaccines which meets the novelty requirements of the statute. For this reason, patent protection should be granted to promote the useful art of making vaccines.

Respectfully submitted,

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9. Appendix

Claims 1, 10-11, 19-24, 26-35, 37-41, 47, 49, 51, 54 and 55 as follows:

1. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide ,on a weight basis relative to said LPS, said peptide comprising:
(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;
(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

10. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide ,on a weight basis relative to said LPS wherein the peptide comprises:
$(Lys\text{-}Phe)_5$ (SEQ ID NO: 5).

11. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
Lys-Phe-Leu-Lys-Lys-Thr-Leu (SEQ ID NO: 6).

12. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:

$(Lys\text{-}Phe\text{-}Leu)_2\text{-}Lys$ (SEQ ID NO: 7)

13. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
$(Lys\text{-}Phe\text{-}Leu)_3\text{-}Lys$ (SEQ ID NO: 8)

14. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
$(Arg\text{-}Tyr\text{-}Val)_3$ (SEQ ID NO: 9)

15. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
$(Lys\text{-}Phe\text{-}Phe)_3\text{-}Lys$ (SEQ ID NO: 10)

16. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
$(Lys\text{-}Leu\text{-}Leu)_3$ (SEQ ID NO: 11)

17. (twice amended) A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
$(Lys)_6(Phe\text{-}Lys)_2$ (SEQ ID NO: 12)

19. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:

Cys-Lys-Phe-Lys-Lys-Cys
 s-------------------s (SEQ ID NO: 14)

20. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:

Lys-Phe-Lys-Cys-Lys-Phe-Lys-Phe-Lys-Cys
 s-----------------------s (SEQ ID NO: 15)

21. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:

Lys-Leu-Lys-Cys-Lys-Leu-Lys-Leu-Lys-Cys
 s-----------------------s (SEQ ID NO: 16)

22. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:

Arg-Thr-Arg-Cys-Arg-Phe-Lys-Arg-Arg-Cys
 s-----------------------s (SEQ ID NO: 17)

23. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide

comprises:
Lys-Cys-$(Lys-Phe-Lys)_2$-Cys-Lys
s------------------s (SEQ ID NO: 18)

24. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
Cys-$(Lys)_4$-$(Phe)_4$-Cys
s------------------s (SEQ ID NO: 19).

26. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
Val-Lys-Ala-Leu-Arg-Val-Arg-Arg-Leu (SEQ ID NO: 21).

27. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
Lys-Ser-Leu-Ser-Leu-Lys-Arg-Leu-Thr-Tyr-Arg (SEQ ID NO:22).

28. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide comprises:
Lys-Val-Arg-Lys-Ser-Phe-Phe-Lys-Val (SEQ ID NO: 23).

29. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide

comprises:
Phe-Leu-Lys-Pro-Gly-Lys-Val-Lys-Val (SEQ ID NO: 24).

30. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:
Lys-Glu-Leu-Lys-Arg-Ile-Lys-Ile (SEQ ID No: 25)

31. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:
Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu (SEQ ID NO: 26)

32. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:
Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu-Lys (SEQ ID NO: 27)

33. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:
Lys-Arg-Leu-Lys-Trp-Lys-Tyr-Lys-Gly-Lys-Phe (SEQ ID NO:28)

34. A vaccine for preventing-gram negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Lys-Thr-Lys-Cys-Lys-Phe-Leu-Lys-Lys-Cys(SEQ ID NO:31)
s - - - - - - - - - - - - s.

35. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Cys-Lys-Phe-Leu-Lys-Lys-Cys
s----------s (Seq ID NO: 30).

37. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Lys-Phe-Leu-Lys-Lys-Thr(SEQ ID NO: 32).

38. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Cys-Lys-Lys-Leu-Phe-Lys-Cys-Lys-Thr-Lys
s - - - - - - - - - - - - s(SEQ ID NO: 33).

39. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Cys-Lys-Lys-Leu-Phe-Lys-Cys-Lys-Thr
s - - - - - - - - - - - - s(SEQ ID NO: 34).

40. A vaccine for preventing gram-negative infections which

comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Ile-Lys-Thr-Lys-Cys-Lys-Phe-Leu-Lys-Lys-Cys
s - - - - - - - - - - - s(SEQ ID NO: 35).

41. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Ile-Lys-Thr-Lys-Lys-Phe-Leu-Lys-Lys-Thr(SEQ ID NO: 36).

47. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

$(Lys)_6$Phe-Leu-Phe-Leu(SEQ ID NO:42).

49. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS wherein the peptide is of the formula:

Lys-Trp-Lys-Ala-Gln-Lys-Arg-Phe-Leu-Lys(SEQ ID NO: 44).

51. A method for the preparation of a vaccine for prevention of gram-negative infections, said method comprising combining LPS with a stoichiometric excess of a peptide on a weight basis relative to said LPS comprising:

(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;

(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a

hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

54. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of peptide:LPS where there is an excess of from 2 to 5000 times by weight of peptide, said peptide comprising:
(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;
(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

55. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS in a free form or in conjugate form with a stoichiometric excess of a peptide on a weight basis relative to said LPS of the formula:
Cys-$(Lys)_5$-Cys
s----------s (SEQ ID NO: 13)

57. A vaccine as defined in claim 1 wherein the LPS is derived from N. meningtidis, H. influenzae, Moraxella catharralis, Pseudomonas aeruginosa, Salmonella enterica and Escherichia

coli.

58. A vaccine as defined in claim 57 wherein the LPS is derived from Salmonella enterica.

59. A vaccine as defined in claim 57 wherein the LPS is derived from H. influenzae.

60. A vaccine as defined in claim 57 wherein the LPS is derived from N. meningtidis.

61. A vaccine as defined in claim 57 wherein the LPS is derived from Moraxella catharralis.

62. A vaccine as defined in claim 57 wherein the LPS is derived from Escherichia coli.

63. A vaccine for preventing gram-negative infections which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric excess of peptide:LPS where there is an excess of from 2 to 2500 times by weight of peptide, said peptide consisting essentially of:
(a) $(A)_n$ wherein A is Lysine or Arginine and n is an integer with a minimum value of 7;
(b) $(AB)_m$ wherein A is Lysine or Arginine and B is a hydrophobic amino acid selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; m is an integer with a minimum value of 3; and (c) $(ABC)_p$ wherein A is a cationic amino acid which is Lysine or Arginine; B and C are hydrophobic amino acids which may be the same or different and are selected from the group consisting of Valine, Leucine, Isoleucine, Tyrosine, Phenylalanine and Tryptophan; p is an integer with a minimum value of 2.

64. A vaccine for preventing gram-negative infections as defined in claim 63 which comprises a complex obtained by combining LPS free or in conjugate form with a stoichiometric

excess of peptide:LPS where there is an excess of from 250 to 2500 times by weight of peptide.